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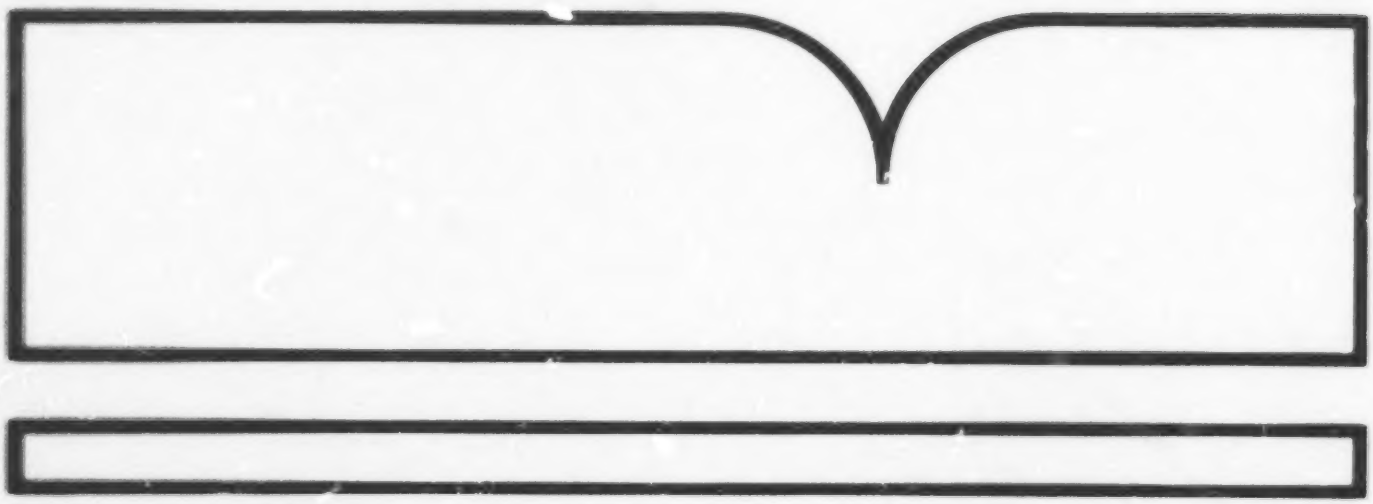

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16. ABSTRACT

This paper presents structure-activity relationships (QSAR) for estimating the bioconcentration factor and acute toxicity of some classes of industrial chemicals using only the n-octanol/water partition coefficient (Log P) which is derived from chemical structure. The bioconcentration factor is estimated by the equation:

$\text{Log BCF} = 0.79 \text{ Log P} - 0.40 \quad r = 0.93 \quad n = 122$

The acute toxicity of polar narcotic chemicals to fathead minnows were substantially greater than non-polar narcotics. Although a comprehensive model is not yet discernable, industrial esters and diesters can be estimated by the equation:

$\text{Log LC50} = -0.535 \text{ Log P} - 2.75 \quad r = 0.91 \quad n = 29$

Guidelines for selecting tests for ecotoxicity assessments are also presented.

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Structure–Activity Relationships for Screening Organic Chemicals for Potential Ecotoxicity Effects*

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I. INTRODUCTION

Two of the important pieces of information needed to evaluate the environmental hazards posed by organic industrial chemicals are the potential for residue bioaccumulation in the food chain and the potential for significant adverse biological activity in aquatic organisms. We have selected the bioconcentration factor test [1] and the 96-h acute toxicity test [2] for fathead minnows as experimental techniques to provide the aforementioned information for aquatic organisms. Having selected these two endpoints, our research has been directed toward developing structure-activity relationships (SAR) which permit the bioconcentration factor and acute toxicity to be estimated directly from chemical structure, and leads into development of a clear understanding of how the two endpoints may be interpreted in a comprehensive hazard assessment. The development of SAR has been separated into the development of structure-bioconcentration relationships and structure-toxicity relationships. The object of this paper is to summarize progress on these two areas of research.

At the outset, it is important to emphasize that SAR development may vary from general qualitative statements to specific quantitative structure-activity relationships (QSAR). SAR are mathematical relationships between measurable behaviors of a chemical and its structure which permit one to predict the behavior of similar untested chemicals with a specified reliability. Decisions concerning the level of "predictability" of a SAR generally come from cost-benefit analysis of the problem being addressed. Thus, SAR development is an optimization process which focuses limited resources on the evaluation of chemicals which pose the greatest hazard to the environment. The SAR development discussed herein is directed at distinguishing structures which should be thoroughly tested from those that should not, and is not directed at prediction of ultimate environmental effects.

II. BIOCONCENTRATION FACTOR

The bioconcentration factor is a proportionality factor relating the residue concentration in aquatic organisms to the water concentration when a steady-state condition exists. The acceptance of the concept of a bioconcentration *factor* is really an acceptance that residues in fish are a direct function of the chemical in water over a wide range of concentration. Methods for measuring the bioconcentration factors have been discussed elsewhere [1, 3].

Because a bioconcentration test costs approximately $6,000-$10,000 for each chemical, it is essential that any regulatory decisions involving such testing have a firm technical basis for suspecting that the chemical will bioconcentrate above ambient levels. Despite the value of a bioconcentration factor in assessing food chain exposure for bioaccumulative chemicals, the test would be a complete waste of $6,000-$10,000 if the chemical did not bioaccumulate. With 1200 new chemicals being evaluated each year, the costs for this one test are significant.

We have reported a structure-bioconcentration relationship [1] in which the bioconcentration factor can be estimated from the equation

$$\log BCF = 0.85 \log P - 0.70 \qquad r = 0.947 \qquad n = 59$$

where BCF is the bioconcentration factor, and P is the n-octanol/water partition coefficient of the chemical. When 122 chemicals were included in the data base, the structure-bioconcentration relationship changed slightly to [3]

$$\log BCF = 0.79 \log P - 0.40 \qquad r = 0.927$$

McKim et al. [4] have shown that the coefficient of this SAR is reasonable based on pharmacokinetic models of transport across trout gills.

The link between this empirical relationship and chemical structure is the method to calculate log P from structure. Leo and Weininger of the Pomona College Medicinal Chemistry Project have developed CLOGP Version 3.2 for this purpose [5]. The log P values of the 20,000 discrete organic industrial chemicals currently in production have been computed by CLOGP Version 3.2. Figure 1 presents a frequency distribution of log P values for industrial chemicals which shows that almost 50% of the chemicals have log P values less than 2.0. The calculated bioconcentration factors for such chemicals are so low that bioaccumulation could not be a major concern. Unless a chemical has exceptional biological activity, it is unlikely that chemicals with log P less than 4.0 could bioaccumulate to hazardous levels in human food chains. If such a hypothesis were generally accepted, Fig. 1 illustrates that bioconcentration testing costs could be reduced by more than 70% if the log P were first computed. Moreover, the design of new chemicals can be directed to eliminate chemicals with log P greater than 4.0 when substantial biological activity is likely.

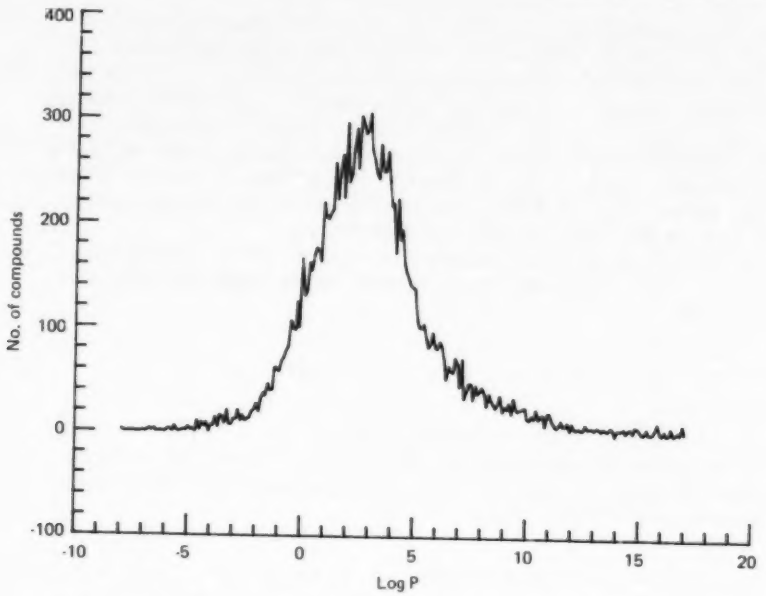

FIG. 1. Frequency distribution of log P values for industrial chemicals.

III. ACUTE TOXICITY

In the development of structure-activity relationships, it is generally true that a separate QSAR can be developed for each mechanism involved in the activity of interest. For structure-toxicity relationships, this means that separate QSAR must be developed for each mode of toxic action. For example, measuring lethal concentrations with a 96-h acute toxicity test leads to the need for separate relationships for chemicals that are lethal by action on the central nervous system, respiratory uncoupling, narcosis, etc. Predicting the LC_{50} of a untested chemical requires the ability to predict the mode of toxic action (selectivity) as well as the QSAR to estimate the activity (toxicity) from structure.

We have observed that the majority of organic industrial chemicals do not have specific structural features which make them biologically active by specific mechanisms. Contrary to drugs or pesticides, industrial chemicals are usually designed for purposes

other than biological activity, and toxicity is most often an unfortunate side effect. The absence of structural features which cause a chemical to have specific effects means that the chemical falls into a large category of chemicals which can be lethal by a nonspecific mode of action called "narcosis." Narcosis is a retardation of normal physiological processes caused by the absorption of foreign molecules into biological membranes. Inert gases, aliphatic and aromatic hydrocarbons, chlorinated hydrocarbons, alcohols, ethers, ketones, weak acids and bases, and some aliphatic nitrocompounds have been shown to cause narcosis.

The frequent occurrence of narcotic chemicals in the TSCA industrial inventory led us to develop a structure-toxicity relationship for this large category. The QSAR to estimate the 96-h LC_{50} is [2]

$$\log LC_{50} = -0.94 \log P + 0.94 \log(0.000068 P + 1) - 1.25$$

The QSAR is a bilinear equation involving only log P, which is consistent with the nonspecific mode of action. This QSAR accurately estimates the 96-h LC_{50} for fathead minnows over the range of 0.1 to 20,000 mg/L. The importance of the bilinear relationship is that the QSAR can be directly related to a structure-water solubility relationship. The toxicity and solubility models intersect at log P 5.5, which predicts that narcotic chemicals with a log P greater than 5.5 will not cause lethality to aquatic organisms, even in a saturated solution of the chemical. Examples of such chemicals selected from the TSCA inventory for testing and shown to be nonlethal at solubility are presented in Table 1. In general, chemicals consisting primarily of carbon and with isolated heteroatoms or functional groups become nonlethal when the number of carbons exceeds 12-14 carbons (unless a highly polar function group reduces the log P below 5.5).

To address the concern that predicting nonlethality does not give assurances that chronic effects would not be caused by the chemical, we must go back to the first section of this paper. Clearly, chemicals with log P greater than 5.5 would be expected to have a substantial bioaccumulation potential. Such a chemical should be evaluated for bioaccumulation in the food chain and for chronic effects of the persistent residues, and this judgment can be made independent of the acute toxicity prediction. To predict that a chemical would not be lethal in a saturated solution only suggests that the $2,000-$3,000 needed for testing acute toxicity should not be wasted on such a test.

Because of the high cost of testing for chronic toxicity, it is unlikely that enough chemicals can be tested to develop a comprehensive set of QSAR on chronic endpoints. We have adopted the use of

TABLE 1

Industrial Chemicals Which are Nonlethal in Saturated Solutions

9,10-Dichloroanthracene
Fluoranthene
p-Terphenyl
2,5-Diphenyl-3-pentanone
n-Nonylbenzene
Hexamethylbenzene
Hexachlorobenzene
1,10-Dichlorodecane
Hydrocarbon above decane
Alcohols above tridecanol
Dioctylether
Aliphatic esters with more than 12 carbons
4-Chloro-m-tolylbenzoate
Dioctylphthalate

the acute test as the initial indication of biological activity and the simultaneous development of chronicity factors for major classes of chemicals and chronic endpoints. To accomplish this, representative chemicals are tested with 28-day embryo-larval chronic tests and pairwise correlation analyses for the chronic toxicity, and acute toxicity provides a chronicity factor. The first of such models has been presented [6] and it shows that the QSAR for lethality for narcotics can be used to estimate the chronic "no-effect" concentration by dividing the LC_{50} by 12.

IV. TOXICITY OF INDUSTRIAL ESTERS

The QSAR used to estimate 96-h LC_{50} for narcotic chemicals [2] is currently considered to be an estimate of baseline toxicity. Chemicals which have specific toxic effects on respiration, the nervous

TABLE 2

96-h LC_{50} Values for Industrial Esters

Chemical	LC_{50} (mg/L)	Log LC_{50} (mol/L)	Log P
2-Ethoxyethyl acetate	42.2	-3.50	0.71
Ethyl-p-aminobenzoate	35.2	-3.67	1.22
Methyl-2,4-dihydroxybenzoate	38.5	-3.64	1.59
Methyl-p-nitrobenzoate	23.6	-3.88	2.10
Methyl-p-chlorobenzoate	10.9	-4.19	3.15
Methyl-4-chloro-2-nitrobenzoate	27.2	-3.90	2.35
Methyl-2,5-dichlorobenzoate	13.8	-4.17	3.45
Ethyl salicylate	19.6	-3.93	3.45
Diethyl-o-phthalate	30.0	-3.87	2.69
Dibutyl adipate	3.66	-4.85	3.96
Methyl acetate	3.20	-2.36	0.18
Ethyl acetate	2.30	-2.58	0.69
Propyl acetate	60.0	-3.23	1.25
Butyl acetate	18.0	-3.81	1.79
Hexyl acetate	4.40	-4.52	2.87
Diethyl adipate	19.3	-4.02	1.80
Diethyl malonate	14.9	-4.03	1.19
Ethyl hexanoate	8.90	-4.21	2.87
Dibutyl succinate	4.45	-4.71	3.65
Diethyl sebacate	2.75	-4.97	3.96
Di-n-butyl-o-phthalate	1.10	-5.40	4.74
Di-n-butyl-m-phthalate	0.90	-5.48	4.74
Diphenyl-o-phthalate	0.80	-5.59	5.07
Dimethyl-2-nitro-p-phthalate	6.52	-4.56	2.28
Dimethyl-2-amino-p-phthalate	8.94	-4.05	2.65
Di-2-ethylhexyl-o-phthalate	Not lethal	–	7.06
Di-n-octyl-o-phthalate	Not lethal	–	7.06
Di-n-octyl-m-phthalate	Not lethal	–	7.06
Di-n-octyl-p-phthalate	Not lethal	–	7.06

system, or enzymes may be more toxic than predicted from the QSAR. Obviously, the acute toxicity cannot be less than predicted by the baseline narcosis QSAR. Despite the wide range of chemical classes which are lethal through narcosis, we have found several classes of industrial chemicals which cause classical narcosis symptoms leading to lethality but have slightly greater acute toxicity than predicted from the baseline narcosis QSAR. One major class of these chemicals are esters, including benzoates, adipates, phthalates, simple salicylates, and alkyl acid esters.

Table 2 presents the 96-h LC_{50} values and log P values for 29 esters using the testing methods described by Veith et al. [2]. The data are consistent with the baseline narcosis model in that esters with log P values greater than about 5.5 are not lethal in saturated solutions. The esters with log P values between 4.0 and 5.5 are reasonably well estimated from the baseline OSCAR; however, the more polar esters are substantially more toxic than estimated. For example, the log molar LC_{50} of di-n-butyl-o-phthalate computed from the baseline narcosis is -5.07, compared to the observed LC_{50} of -5.40 (Table 2). In contrast, 2-ethoxyethyl acetate would have an estimated toxicity of -1.92, and the observed LC_{50} was -3.50.

The data presented in Table 2 were included in a linear regression using log P and the independent variable. The resulting QSAR for esters is

$$\log LC_{50} = -0.535 \log P - 2.75$$

where $n = 29$ and $r^2 = 0.828$. This QSAR should not be used for esters with log P values greater than 5.5. This regression analysis differs from baseline narcosis toxicity in that the log P account for less of the variance in the toxicity, as evidenced by the lower coefficient. The QSAR could presumably be improved by adding an orthogonal electronic parameter to account for the increased polarity or reactivity of esters. However, we have not yet discovered a meaningful second molecular descriptor to improve the standard error of the estimate for esters.

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